Recombinant Factor VIIa for Intracerebral Hemorrhage

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University Health Network
Outline

1. Introduction to patient case

2. Overview of intracerebral hemorrhage (ICH)
   a. Presentation
   b. Risk factors
   c. Medical management

3. Overview of recombinant Factor VIIa
   a. Efficacy
   b. Safety

4. Apply EBM principles to patient case
Overview of Patient Case
Mr. ICH

- 58 year old male of African descent

- HPI:
  - Sudden onset of severe headache, nausea and left-sided weakness
  - After wife called 911, patient began to have slurred speech, vomited and then collapsed
  - On admission, BP 190/95, HR 52, GCS 7
Mr. ICH

- At 3 h from onset,
  - head CT confirms ICH in the right putamen
    - Mild hydrocephalus and slight left midline shift
Mr. ICH

PMH:

- Hypertension
- Hyperlipidemia
- DVT (1 year ago)
- Type II Diabetes
- Smoker (1 pack per day)
Mr. ICH

BPMH:

- Hydrochlorothiazide 25 mg po OD
- Ramipril 5 mg po OD
- Atorvastatin 40 mg po OD
- Metformin 1000 mg po BID
Clinical Question

- Is recombinant Factor VII (rFVIIa) a reasonable therapeutic alternative in Mr. ICH?
  - Will it improve his clinical outcome?
  - Is it safe to use in the treatment of ICH given his past medical history?
Overview of Intracerebral Hemorrhage (ICH)
Clinical Presentation

- **Bleeding due to a ruptured intracranial vessel**
  - Focal neurological deficit
  - Sudden onset
  - Progresses over minutes to hours

- **Signs and Symptoms**
  - ± Headache
  - ± Nausea / Vomiting
  - ± ↓ LOC
  - ± ↑ BP
Causes and Risk Factors

- **Primary (80-85%)**
  - Sustained hypertension
  - Cerebral amyloid angiopathy

- **Secondary (15-20%)**
  - Trauma
  - Aneurysms
  - Arteriovenous malformations (AVMs)
  - Coagulopathies
  - Use of anticoagulants, antiplatelets or thrombolytics
  - Illicit drug use
  - Alcohol
Treatment Guidelines

Lack of proven medical or surgical treatment!
Medical Management

- Airway and oxygenation
- Manage blood pressure
- Manage intracranial pressure
- Maintain euvolemia
- Prevent seizures
- Treat hyperthermia
Morbidity and Mortality

- Mortality at 1 month is 35-52%
  - Half of the deaths occur within first 2 days

- Only 20% of survivors regain functional independence

Hematoma Growth

- ICH is a dynamic phenomenon
  - Result of ongoing bleeding or rebleeding
    - 38% of ICH patients exhibit hematoma growth (volume increase >33%) within 24 hours

- Early hematoma growth is associated with neurological deterioration

- Hematoma volume is determinant of mortality and functional outcome

Davis SM et al. Neurology 2006; 66: 1175-81
Hypothesis

- Risk of disability or death can be reduced by treatments that:
  - promote clotting
  - arrest bleeding
  - minimize hematoma growth
Overview of Recombinant Factor VIIa (rFVIIa)
NovoSeven® (rFVIIa)

- rFVIIa induces hemostasis at site of injury
  - Binds to exposed tissue factor (TF)
  - Binds to activated platelets
    - Result? Formation of thrombin

- Good safety profile in patients with hemophilia and other bleeding disorders

- Hemostatic benefits may be offset by thromboembolic adverse events
rFVIIa-Tissue Factor Complex

rFVIIa-TF complex activates Factor IX and Factor X
Direct Activation of Factor X

Platelets are activated by initial thrombin generated by rFVIIa

rFVIIa directly activates Factor X on the surface of an activated platelet
“Thrombin Burst”

Factor Xa, in complex with other factors, converts prothrombin (Factor II) to thrombiin (Factor IIa)

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Formation of Fibrin Clot

Thrombin leads to formation of a hemostatic plug by converting fibrinogen to fibrin

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Literature Search Results

- **3 Phase II RCTs to date**
  - rFVIIa EurAsia IIA
  - rFVIIa USA IIA
  - rFVIIa IIB

- **All compare various rFVIIa doses to placebo**

- **All studies funded by NovoNordisk®**
rFVIIa EurAsia IIA

Safety and Feasibility of Recombinant Factor VIIa for Acute Intracerebral Hemorrhage

Stephan A. Mayer, MD; Nikolai C. Brun MD, PhD; Joseph Broderick, MD; Stephen Davis, MD; Michael N. Diringer, MD; Brett E. Skolnick, PhD; Thorsten Steiner, MD;
for the Europe/AustralAsia NovoSeven ICH Trial Investigators

Stroke 2005; 36: 74-9
rFVIIa EurAsia IIA

- Dose escalation trial
- Multicenter, randomized, double-blind, placebo-controlled
- 48 patients

- rFVIIa 10, 20, 40, 80, 120 or 160 µg/kg vs. placebo

- Primary endpoint was frequency of AEs
rFVIIa EurAsia IIA

- rFVIIa was well tolerated
  - 6 possible treatment-related AEs
    - 2 DVTs (in placebo and 20 µg/kg)

- No noticeable differences in types, frequency or severity of AEs

- Most common AEs included:
  - Fever
  - Headache
  - UTI
  - Hypertension
  - Constipation
Recombinant Activated Factor VII for Acute Intracerebral Hemorrhage

US Phase IIA Trial

Stephan A. Mayer,1,∗ Nikolai C. Brun,2 Joseph Broderick,3 Stephen M. Davis,4 Michael N. Diringer,5 Brett E. Skolnick,6 Thorsten Steiner,7 for the United States NovoSeven ICH Trial Investigators

1Departments of Neurology and Neurosurgery, Columbia University College of Physicians & Surgeons, New York, NY; 2Novo Nordisk A/S, Bagsvaerd, Denmark; 3The University Of Cincinnati Medical Center, Cincinatti, OH; 4Royal Melbourne Hospital, University of Melbourne, Melbourne, Australia; 5Washington University School of Medicine, St. Louis, MO; 6Novo Nordisk, Princeton, NJ; and 7University of Heidelberg, Heidelberg, Germany

Neurocrit Care 2006; 04: 206-14
rFVIIa USA IIA

- Dose-escalation trial
- Multicenter, randomized, double-blind, placebo-controlled
- 40 patients

- rFVIIa 5, 20, 40, or 80 µg/kg vs. placebo

- Primary endpoint was frequency of AEs
rFVIIa USA IIA

- rFVIIa was well tolerated
  - 12 possible or probable treatment-related AEs
    - None were thromboembolic AEs

- No significant differences in types, frequency or severity of AEs

- Most common AEs included:
  - UTI
  - Fever
  - Constipation
  - Somnolence
rFVIIa IIB Trial

Recombinant Activated Factor VII for Acute Intracerebral Hemorrhage

Stephan A. Mayer, M.D., Nikolai C. Brun, M.D., Ph.D., Kamilla Begtrup, M.Sc., Joseph Broderick, M.D., Stephen Davis, M.D., Michael N. Diringer, M.D., Brett E. Skolnick, Ph.D., and Thorsten Steiner, M.D., for the Recombinant Activated Factor VII Intracerebral Hemorrhage Trial Investigators*

rFVIIa IIb

- Multicenter (73 hospitals, 20 countries)
- Double-blind, placebo-controlled
- 399 patients

Intervention:
- Single IV dose of rFVIIa 40, 80 or 160 µg/kg vs. placebo
  - N= 108 (40 µg)
  - N= 92 (80 µg)
  - N= 103 (160 µg)
  - N= 96 (placebo)

Primary Endpoint:
- % change in volume of ICH at 24 hours
- Clinical outcomes at 90 days
## rFVIIa IIB Trial

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ ≥ 18 years of age</td>
<td>▪ GCS 3-5</td>
</tr>
<tr>
<td>▪ CT confirmed ICH within 3 h of onset</td>
<td>▪ Planned surgical evacuation with 24 h</td>
</tr>
<tr>
<td></td>
<td>▪ ICH secondary to aneurysm, AVM, trauma or other cause</td>
</tr>
<tr>
<td></td>
<td>▪ Use of oral anticoagulants</td>
</tr>
<tr>
<td></td>
<td>▪ Thrombocytopenia</td>
</tr>
<tr>
<td></td>
<td>▪ History of coagulopathy, acute sepsis, crush injury or DIC</td>
</tr>
<tr>
<td></td>
<td>▪ Pregnancy</td>
</tr>
<tr>
<td></td>
<td>▪ <strong>Symptomatic</strong> thrombotic or vaso-occlusive disease (i.e. angina, claudication, DVT, or cerebral or myocardial infaction)</td>
</tr>
</tbody>
</table>

Note: Patient with ANY history of thrombotic or vaso-occlusive disease were excluded midway through the trial due to safety concerns

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### Results of rFVIIa IIB

<table>
<thead>
<tr>
<th>Outcome at 24 h</th>
<th>40 µg/kg</th>
<th>80 µg/kg</th>
<th>160 µg/kg</th>
<th>Combined</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesion Volume of ICH (mL)</td>
<td>5.4</td>
<td>4.2</td>
<td>2.9</td>
<td>4.2</td>
<td>8.7</td>
</tr>
<tr>
<td>Difference in Mean Volume Increase from Baseline (98.3% CI)</td>
<td>3.3 (1.9 to 8.5)</td>
<td>4.5 (0.8 to 9.9)</td>
<td>5.8 (0.6 to 11)</td>
<td>4.5 (0.2 to 8.8)</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>0.13</td>
<td>0.04</td>
<td>0.008</td>
<td>0.01</td>
<td></td>
</tr>
</tbody>
</table>

Reduction in hematoma volume was only significant at the highest dose.
Results of rFVIIa IIB

Note: Study was not adequately powered to detect difference of TE events
Clinical Outcomes

<table>
<thead>
<tr>
<th>rFVIIa</th>
<th>Modified Rankin Scale</th>
<th>Barthel Index</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0–1</td>
<td>2–3</td>
</tr>
<tr>
<td>160 µg/kg</td>
<td>24</td>
<td>21</td>
</tr>
<tr>
<td>80 µg/kg</td>
<td>21</td>
<td>29</td>
</tr>
<tr>
<td>40 µg/kg</td>
<td>17</td>
<td>29</td>
</tr>
<tr>
<td>Placebo</td>
<td>8</td>
<td>23</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>rFVIIa</th>
<th>Extended Glasgow Outcome Scale</th>
<th>NIH Stroke Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>7–8</td>
<td>5–6</td>
</tr>
<tr>
<td>160 µg/kg</td>
<td>15</td>
<td>11</td>
</tr>
<tr>
<td>80 µg/kg</td>
<td>13</td>
<td>15</td>
</tr>
<tr>
<td>40 µg/kg</td>
<td>11</td>
<td>16</td>
</tr>
<tr>
<td>Placebo</td>
<td>6</td>
<td>12</td>
</tr>
</tbody>
</table>

Figure 2. Outcome at 90 Days According to Study Group.

All scales show more favourable outcome with rFVIIa in dose-response trend. Results significant for all doses in modified Rankin and NIH Stroke Scales.

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## Clinical Outcomes

<table>
<thead>
<tr>
<th>Outcome at 90 d</th>
<th>rFVIIa (Combined Doses)</th>
<th>Placebo (98.3% CI)</th>
<th>RRR (98.3% CI)</th>
<th>NNT (98.3% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>18%</td>
<td>29%</td>
<td>37% (6 to 57)</td>
<td>10 (5 to 82)</td>
</tr>
<tr>
<td>Unfavourable Outcome</td>
<td>53%</td>
<td>69%</td>
<td>23% (8 to 35)</td>
<td>7 (4 to 22)</td>
</tr>
<tr>
<td>(Death or Severe Disability)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Safety of rFVIIa

<table>
<thead>
<tr>
<th>Serious Thrombo-embolic Adverse Events</th>
<th>40 µg/kg</th>
<th>80 µg/kg</th>
<th>160 µg/kg</th>
<th>Combined</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>7 (6%)</td>
<td>4 (4%)</td>
<td>10 (10%)</td>
<td>21 (7%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Arterial</td>
<td>6 (6%)</td>
<td>2 (2%)</td>
<td>8 (8%)</td>
<td>16 (5%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Venous</td>
<td>1 (1%)</td>
<td>2 (2%)</td>
<td>2 (2%)</td>
<td>5 (2%)</td>
<td>2 (2%)</td>
</tr>
</tbody>
</table>
Safety of rFVIIa

- Apparent 3x increase in thromboembolic events in the combined rFVIIa group
  - RR 3.33, 95% CI 0.79 to 13.93
    - Reduction or increase?

- Underestimation of risks of using rFVIIa?
  - Recall exclusion of patients with recent history of thrombotic or vaso-occlusive disease
Do These Results Apply?

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo (N=96)</th>
<th>Placebo (N=108)</th>
<th>Placebo (N=92)</th>
<th>Placebo (N=103)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>68±12</td>
<td>67±12</td>
<td>65±12</td>
<td>64±13</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>53</td>
<td>63</td>
<td>61</td>
<td>67</td>
</tr>
<tr>
<td>Race or ethnic group (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>81</td>
<td>77</td>
<td>86</td>
<td>80</td>
</tr>
<tr>
<td>Asian or Pacific Islander</td>
<td>15</td>
<td>19</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>Other</td>
<td>4</td>
<td>5</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Location of hemorrhage (%)†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Putamen or globus pallidus</td>
<td>58</td>
<td>54</td>
<td>44</td>
<td>55</td>
</tr>
<tr>
<td>Thalamus</td>
<td>30</td>
<td>33</td>
<td>40</td>
<td>31</td>
</tr>
<tr>
<td>Lobar hemisphere</td>
<td>21</td>
<td>18</td>
<td>25</td>
<td>18</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>2</td>
<td>4</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Pons or midbrain</td>
<td>6</td>
<td>4</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>GCS score‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>14</td>
<td>14</td>
<td>15</td>
<td>14</td>
</tr>
<tr>
<td>NIHSS score§</td>
<td>15±6</td>
<td>14±6</td>
<td>12±6</td>
<td>14±6</td>
</tr>
<tr>
<td>Systolic BP at time of treatment (mm Hg)</td>
<td>172±32</td>
<td>170±28</td>
<td>178±32</td>
<td>172±30</td>
</tr>
<tr>
<td>Time from onset to treatment (min)</td>
<td>165±33</td>
<td>173±32</td>
<td>167±32</td>
<td>165±32</td>
</tr>
<tr>
<td>Treated &lt;3 hr after onset (%)</td>
<td>72</td>
<td>62</td>
<td>76</td>
<td>71</td>
</tr>
</tbody>
</table>
Strengths of rFVIIa IIB

- Reduction in hematoma growth is appropriate surrogate outcome
  - Well-established relationship between ICH volume and clinical outcome
  - Volume is independent of hemorrhage location

- Intention-to-treat analysis was performed
Limitations of rFVIIa IIb

- Were baseline characteristics similar?
  - GCS, location of ICH, baseline volume, BP

- Benefit was only significant in patients treated ≤ 3 h after onset
  - At >3 h, mean volume increase was 14% vs. 16% in favour of placebo (p=0.86)
    - Subgroup was underpowered to detect difference

- Reduction in hematoma growth was only statistically significant at 160 µg/kg
Limitations of rFVIIa IIB

- Study was not powered to detect the magnitude of the study’s difference in AEs

- Exclusion criteria were changed midway due to safety concerns
  - 49% of patients had already been enrolled
Application to Mr. ICH

- rFVIIa may not be suitable due to several unanswered questions
  - Acceptable safety profile?
    - prothrombotic risk factors (recent history of DVT)
  - Optimal therapeutic window?
    - treatment after 3 h of ICH onset
  - Fits the study population?
    - African descent
Conclusions

- Early hemostatic therapy with rFVIIa given within **4 hours** of primary spontaneous ICH onset reduces:
  - Hematoma growth
  - Unfavourable outcome at 90 days
  - Mortality at 90 days

- Data is promising, but not clinically directive
  - More evidence is needed to address
    - Safety and prothrombotic risk
    - Optimal treatment window
    - Influence of other prognostic factors
    - Use in other ICH subtypes
Conclusions

Results cannot be generalized to all ICH patients

- Inclusions?
  - Elderly caucasian males who can be treated within 3 h

- Exclusions?
  - ICH due to secondary cause
    - eg. anticoagulant use, aneurysm, AVM, etc.
  - History of thrombotic or vaso-occlusive disease
    - Ischemic stroke
    - Myocardial infarction
    - DVT / PE
    - Claudication
Ongoing Phase III Trial

rFVIIa in Acute Hemorrhagic Stroke Treatment (FAST) trial

- Desired sample size
  - 675 patients

- Intervention
  - rFVIIa (20 µg/kg or 80 µg/kg) vs. placebo

- Primary endpoint
  - death or severe disability at day 90

- Study likely will not have power to detect differences in serious thromboembolic AEs
Discussion & Questions